

REMARKS/ARGUMENTS

Claims 12 and 15-17 are active.

Claim 15 is amended to remove the reference to cancelled Claim 13.

Claim 13 remains rejected under 35 USC 103(a) citing Vuorio in view of Young, Nah, Sandell 1, Sandell 2 and Upholt; and Claims 15-17 remain rejected under 35 USC 103(a) citing Vuorio, Young, Na, Sandell 1, Sandell 2, Upholt and Matsumoto.

In maintaining the rejections, the Examiner inquires as to which moiety of SEQ ID NO: 2 has been disclosed and which moiety has not been disclosed in the papers of Vuorio, Young, Nah, Sandell 1, Sandell 2 and Upholt.

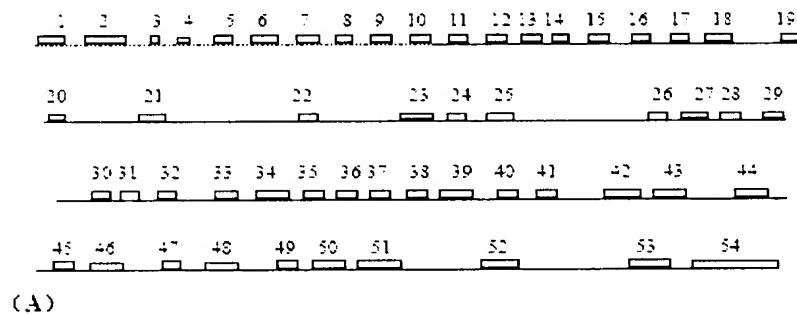
Except for Young, the other five papers of Vuorio, Nah, Sandell 1, Sandell 2 and Upholt, were published by the study group led by the Prof. Upholt and relate to two minor fragments of cDNA and a small part of genome DNA encoding chicken type-II collagen. It is particularly noted that most of the cited 6 papers only describe the length or size of the cloned gene fragments or number of exons but do not disclose any base sequence or peptide sequence. Accordingly, even if it is conceded that some fragments or exons of a chicken type-II collagen gene were cloned in these 6 papers, as the relevant base sequence a chicken type-II collagen gene and the corresponding peptide sequence were not disclosed, the combination of these 6 papers cannot render the claims obvious.

In short, Vuorio, Sandell 1, Sandell 2 and Young at best include portions of the 3'-end of the gene, Upholt at best has some discussion for cloned fragments including part of exon 13 to the 3' end and Nath includes a portion of the gene encompassing exon 2. However, as noted in the depictions below, referencing both the full genomic, exon/intron organization, and the cDNA, the sequences of at least certain 5' end portions are not described.

To more fully understand the differences between the claimed invention and what is described in Vuorio, Young, Nah, Sandell 1, Sandell 2 and Upholt, Applicants provide the following discussion.

As has been discussed previously, the full length cDNA encoding chicken type II collagen has a highly complex structure and it was very difficult to have it isolated and cloned. It was due to the inventors long-term effort that the CCOL2A1 full length cDNA having a length of 4837 bp (it spans 4837 bp with an open reading frame of 4260 bp extending from 45 to 4305 bp, 44bp 5'UTR and 533 bp 3'TR; the deduced peptide of ccol2a1, composed of 1420 amino acids, can be divided into signal peptide, N-propeptide, N-telopeptide, triple helix, C-telopeptide and C-propeptide) was obtained. In addition, the genomic DNA sequence comprising 54 exons and 53 introns and having a length of 12523 bp was cloned by the inventors (see the representation in the Figure 1A-C below). Before the present invention, there was no report about the successful cloning of the full-length cDNA sequence encoding chicken type II collagen and its detailed base sequence or corresponding peptide sequence and as such this is not a case where one simply can piece together various portions of clones, without sequence information, from the results reported in Vuorio, Young, Nah, Sandell 1, Sandell 2 and Upholt.

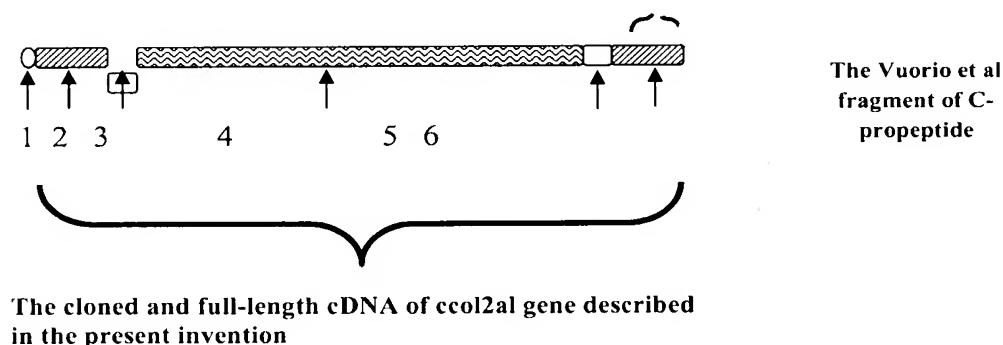
**Fig1. A schematic representation of the exon-intron organization and the structure of the deduced peptide of chicken type II collagen. (A),** Genomic organization of *ccol2a1* gene (not drawn to scale). Gray boxes indicate sequenced exons; horizontal lines indicate introns. **(B),** Schematic representation of the deduced peptide of *ccol2a1* gene: signal peptide, N-propeptide, N-telopeptide, triple helix, C-telopeptide, C-propeptide. **(C),** Schematic representation of the deduced peptide sequence of *ccol2a1* gene.



1. signal peptide    2. N-propeptide    3. N-telopeptide    4. triple helix  
5. C-telopeptide    6. C-propeptide

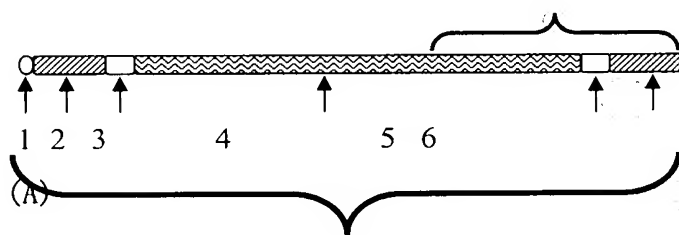
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Vuorio et al only reported that: type II procollagen mRNA was purified from embryonic chick sternal cartilage by guanidine hydrochloride extraction, sucrose gradient sedimentation and Sepharose 4B chromatography; double stranded cDNA was synthesized using AMV reverse transcriptase and inserted into pBR322 vector; and two deduced cDNA, pCAR1 (525bp) and pCAR2 (680bp), were subjected to enzyme cleavage, hybridization and identification by primary sequencing, and the results suggested that these cDNA are complementary to type II procollagen mRNA. Moreover, the two cDNAs only encode small portion of 3'-end of the chicken type II collagen (i.e., C-propeptide) rather than encode the critical triple helix domain of the chicken type II collagen. In particular, pCAR1 (525bp) completely overlaps with pCAR2 (680bp), so that the two cloned fragments substantially refer to same fragment but differ slightly in length from each other. Moreover, the longest size of the two fragments is only 680 bp (see the following figure which is a schematic representation of the deduced peptide of *ccol2a1* gene containing 1.signal peptide, 2.N-propeptide, 3.N-telopeptide, 4.triple helix, 5.C-telopeptide and 6.C-propeptide in proper order and the portion discussed in Vuorio). Furthermore, the base sequences of the small fragments of pCAR1 (525bp) and pCAR2 were not described therein.



Sandell 1 reported that: a genomic sequence LgCOL (II) partially coding for chicken type II procollagen was isolated and identified by screening a  $\lambda$  Charon 4A library using the

two cDNA of type II collagen, i.e., pCAR1 (525bp) and pCAR2 (680bp); and this genomic sequence is a portion of the gene from amino acid 578 of the triple helical region to the COOH-terminal end of the protein (approximately 700 amino acids). Sandell 1 et al only disclose the minor base sequence encoding 578-603aa of the triple helix domain and 7-26aa of the C-telopeptides and corresponding peptide sequence thereof, and a detailed base sequence of the genomic LgCOL (II) encoding chicken type II collagen is not reported in this paper. Even if the genome LgCOL (II) encoding chicken type II collagen was cloned and sequenced by Sandell 1, the corresponding base sequence was not disclosed by Sandell 1. see the graphical depiction below of the regions discussed pertaining to Sandell 1 compared to the full-length gene

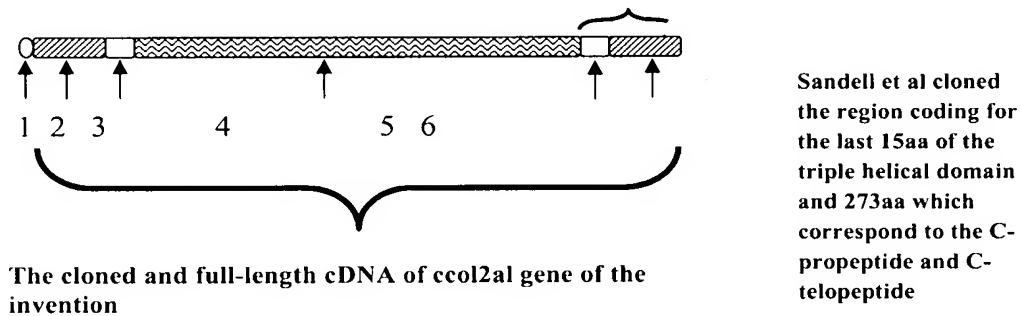


The cloned and full-length cDNA of ccol2a1 gene of the invention

The Sandell et al cloned gene region

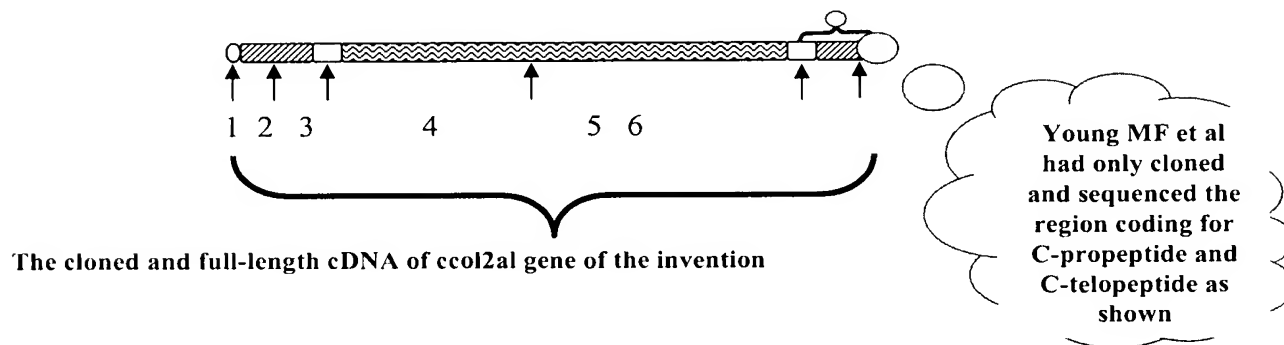
Sandell 2 et al describes the two cDNA of type II collagen (pCAR1 (525bp) and pCAR2 (680bp)) cloned in the Vuorio and Sandell 1 and the genomic sequence LgCOL (II) partially coding for chicken type II procollagen were subjected to further sequence analysis the results of which showed that the three overlapping genes only cover the region consisting

of 4 exons encoding for the last 15 amino acids of the 3'-end domain and 273 amino acids which correspond to the COOH-terminal telopeptide and COOH-terminal propeptide (see the graphical depiction below of the regions discussed pertaining to Sandell 2 compared to the full-length gene). In particular, Sandell 2 et al only discloses the base sequence encoding the last 15 amino acids of the triple helix domain and 273aa which correspond to the COOH-terminal telopeptide and COOH-terminal propeptide and the corresponding peptide sequence thereof.

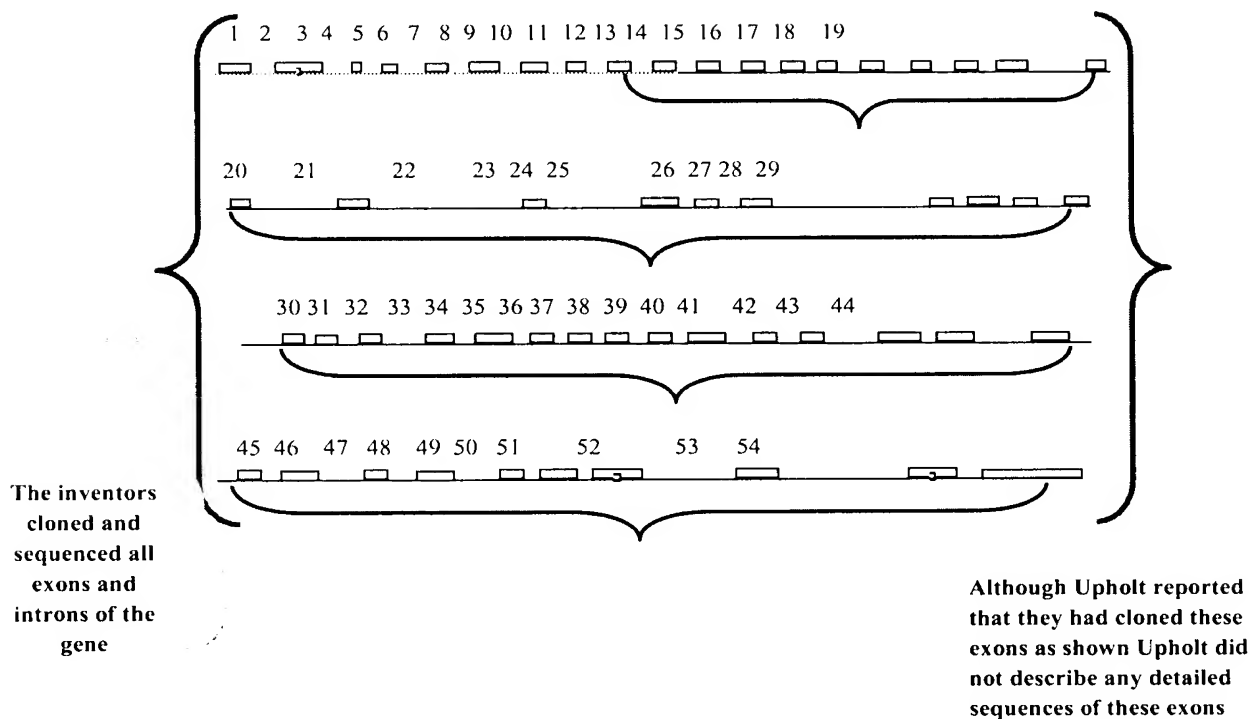


Young et al reported that a cDNA library constructed from total chick embryo RNA was screened with an enriched fraction of type II collagen mRNA; two overlapping cDNA clones (pCs1 (700bp) and pCs2 (1200bp)) encoding the COOH pro-peptide of type II collagen were screened out; pCs1 and pCs2 had 700 base pairs in common; pCs2 extended approximately 500 bp 3' to pCs1; and the two clones pCs1 and pCs2 appeared to overlap the two cDNA pCAR 1 (525bp) and pCAR2 (680bp) obtained by Vuorio et al.; and a genomic sequence partially encoding chicken type II collagen was isolated from a  $\lambda$  Charon 4A library, and the genomic sequence contains the 3' end of the chicken type II collagen gene (see the graphical depiction below of the regions discussed pertaining to Young compared to

the full-length gene). Notably, Young et al only discloses the base sequence of the coding region of C-propeptide and C-telopeptide of chicken type II collagen gene,.

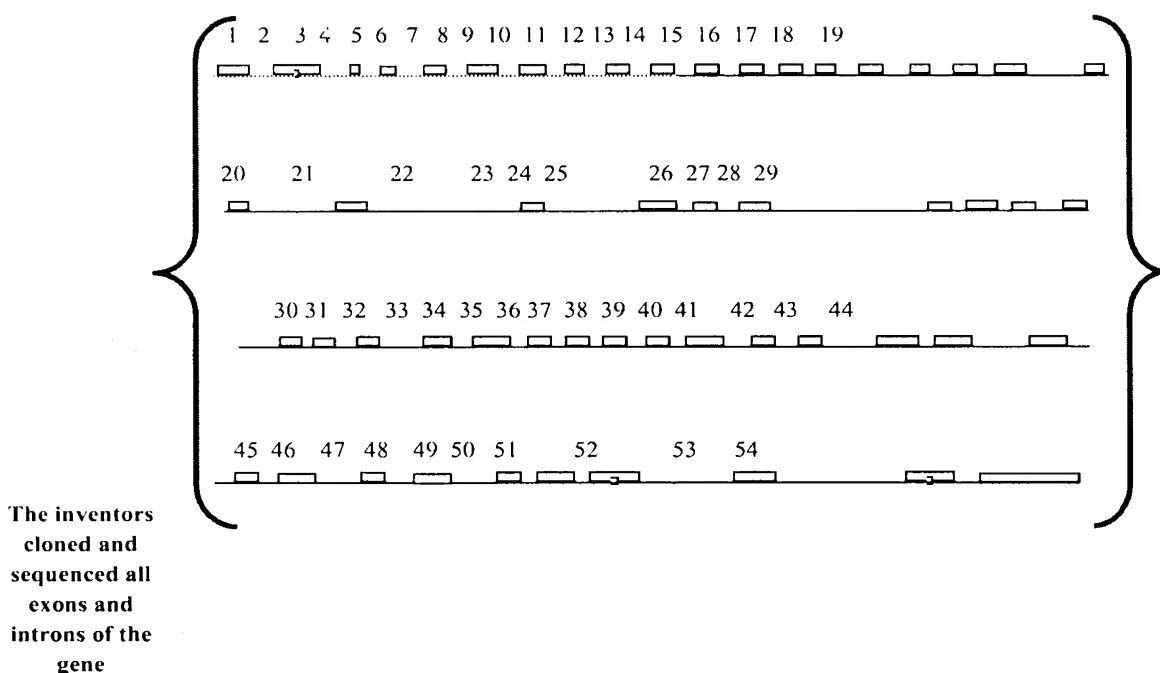
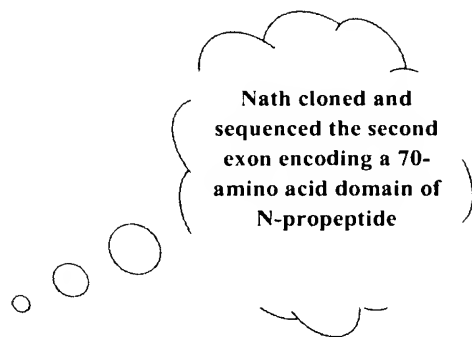


In Upholt et al, the genomic sequence LgCOL (II) partially encoding chicken type II collagen and another genomic sequence LgCOL (II) C-F partially encoding chicken type II collagen was screened out with LgCOL (II) as probe and subjected to sequence analysis to investigate the exon/intron organization of the  $\alpha$ -strand triple helical region of chicken type II procollagen gene (see the graphical depiction below of the regions discussed pertaining to Young compared to the full-length gene). Most particularly, the base sequences of the cloned exons are not reported in Upholt et al. Even if the exons were cloned and sequenced by Upholt et al, the corresponding base sequence of these exons was not disclosed by Upholt et al.



Nath et al reported that the cDNA sequence of the second exon from 5' end of chicken type II collagen gene was cloned and determined, which exon merely encodes 70 amino acids of the 5' end (see the graphical depiction below of the regions discussed pertaining to Nath compared to the full-length gene). It can be seen that the group led by Prof. Upholt took 7 years' hard work to clone and determine the cDNA sequence of the second exon from 5' end of chicken type II collagen gene (only for 85 amino acids and 255 bp bases) on the basis of the cloned and determined cDNA sequence consisting of 4 exons from 3' end of chicken type II collagen, which clearly supports the Applicants position that cloning the gene encoding chicken type II collagen is not as routine and predictable as the rejection concludes.





Accordingly, there is simply not sufficient information regarding the structure and sequence from the combined teachings of the cited publications to render the claims obvious. Withdrawal of the rejection is requested.

Claims 12, 15, and 16 are rejected under 35 USC 101 and under 35 USC 112, first paragraph; Claim 17 is also rejected under 35 USC 101. Specifically, in each of the rejections, the Examiner asserts that SEQ ID NO: 1 does not encode chicken type II collagen.

Application No. 10/534,538  
Reply to Office Action of August 27, 2010

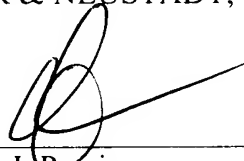
The rejection is no longer applicable as Claim 12 (which recited SEQ ID NO:1) has been cancelled and Claim 15 has been amended to depend only from Claim 12.

Withdrawal of the rejections is requested.

Applicants submit the present application is now in condition for allowance. Early notification to this effect is earnestly solicited.

Respectfully submitted,

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